



With the aid of H. H. Kuhn from the University of Illinois at Urbana-Champaign, we have been able to obtain the following results:

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This application claims priority benefit of Swedish Application No. 9903028-0, filed August 27, 1999, which is incorporated by reference in its entirety.

FIELD OF INVENTION

The present invention relates to use of an inhibitor of the renin-angiotensin system (RAS) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of stroke, diabetes and /or congestive heart failure (CHF). The present invention further relates to a method of prevention and/or treatment of stroke, diabetes and/or CHF, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof to a patient in need of such prevention and/or treatment.

BACKGROUND OF THE INVENTION

Compounds that interfere with the RAS are well known in the art and are used to treat cardiovascular diseases, particularly arterial hypertension and heart failure. Principally, the RAS can be interfered with by inhibition of the enzymes synthesizing angiotensins or by blocking the corresponding receptors at the effector sites. Available today are inhibitors of the angiotensin converting enzyme (ACE) and angiotensin II type 1 receptor (AT II) antagonists.

ACE inhibitors are compounds which inhibit the conversion of angiotensin I into the active angiotensin II as well as the breakdown of the active vasodilator bradykinin. Both of these mechanisms lead to vasodilation. Such compounds have been described in, for example, EP 158927, EP 317878, US 4,743,450, and US 4,857,520.

Ramipril (disclosed in EP-A-079022) is a long-acting ACE inhibitor. Its active metabolite is the free diacid ramiprilat, which is obtained in vivo upon administration of ramipril. In hypertensive patients administration of ramipril is known to cause a reduction in peripheral arterial resistance and thus a reduction of the blood pressure without a compensatory rise in heart rate. It is

Yet another aspect of the invention is a pharmaceutical formulation for use in the prevention of stroke, diabetes and/or CHF, comprising a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof.

A further aspect of the invention is the use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, in the prevention of stroke, diabetes and/or CHF, by administering the inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that cardiovascular and metabolic disorders such as stroke, diabetes and CHF can be prevented by use of an inhibitor of RAS, particularly an ACE inhibitor that interferes with the synthesis of angiotensin II. The present invention is especially surprising in that patients with an essentially maintained heart function and/or exhibiting a normal or low blood pressure benefit markedly from the preventive action of the inhibitors of RAS. The invention describes a new method to prevent disorders such as stroke, diabetes and/or CHF by administration of an inhibitor of the RAS.

Patients exhibiting a normal or low blood pressure are known as normotensive patients. Examples of guidelines defining blood pressure values for different patient groups including different ages, include guidelines issued by the WHO and JNC (USA). In the present invention, a suitable definition of a normal or low blood pressure can be found in JNC VI, which is hereby incorporated by reference.

In the present invention, "stroke" includes both fatal and non-fatal.

In the present invention, "diabetes" include both type I diabetes, also known as insulin-dependent, diabetes mellitus (IDMM), and type II diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM).

In the present invention, "inhibitor of the renin-angiotensin system (RAS) or a pharmaceutically acceptable derivative thereof" includes any compound which in itself or upon administration blocks the negative effects of angiotensin II on the vasculature either by reducing the synthesis of angiotensin II or blocking its effect at the receptor.

In the present invention, "angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable derivative thereof" includes any compound which in itself or upon administration interferes with the synthesis of angiotensin II.

When the inhibitor of the RAS used in the present invention have several asymmetric carbon atoms, they can consequently exist in several stereochemical forms. The present invention includes the mixture of isomers as well as the individual stereoisomers. The present invention further includes geometrical isomers, rotational isomers, enantiomers, racemates and diastereomers.

Where applicable, the inhibitors of RAS may be used in neutral form, e.g. as a carboxylic acid, or in the form of a salt, preferably a pharmaceutically acceptable salt such as the sodium, potassium, ammonium, calcium or magnesium salt of the compound at issue. Where applicable the compounds listed above can be used in hydrolyzable ester form.

In the present invention, the inhibitors of the RAS include all prodrugs thereof, whether active or inactive in vitro. Thus, although such protected derivatives may not possess pharmacological activity per se, they may be administered e.g. parenterally or orally, and thereafter metabolized in vivo to form pharmacologically active inhibitors of RAS. Preferred examples are ramipril, which is metabolized into ramiprilat, and candesartan cilexetil, which is metabolized into candesartan.

Inhibitors of the RAS include ACE inhibitors, AT II antagonists, also known as angiotensin receptor blockers (ARBs), renin antagonists and vasopeptidase inhibitors (VPIs).

The phrase "vasopeptidase inhibitors" embraces so-called NEP/ACE inhibitors (also referred to as selective or dual acting neutral endopeptidase inhibitors) which possess neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme (ACE) inhibitory activity.

The term "renin antagonists" embraces rennin inhibitors.

In the present invention, the RAS inhibitors may exhibit a long term duration, medium term duration or short term duration.

ACE inhibitors or pharmaceutically acceptable derivatives thereof, including active metabolites, which can be used for the prevention of stroke, diabetes and/or CHF include, but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat.

Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors

for uses in the present invention are ramipril and ramiprilat. Information about ramipril and ramiprilat can be obtained e.g. from the Merck Index., 12th ed., 1996, pp. 1394-1395.

AT II antagonists or pharmaceutically acceptable derivatives thereof, including active metabolites, which can be used for the prevention of stroke, diabetes and/or CHF include, but is not limited to, those described in European Patent Applications, Publication Nos. 253310, 323841, 324377, 399731, 400974, 401030, 403158, 403159, 407102, 407342, 409332, 411507, 411766, 412594, 412848, 415886, 419048, 420237, 424317, 425211, 425921, 426021, 427463, 429257, 430300, 430709, 432737, 434038, 434249, 435827, 437103, 438869, 442473, 443568, 443983, 445811, 446062, 449699, 450566, 453210, 454511, 454831, 456442, 456442, 456510, 459136, 461039, 461040, 465323, 465368, 467207, 467715, 468372, 468470, 470543, 475206, 475898, 479479, 480204, 480659, 481448, 481614, 483683, 485929, 487252, 487745, 488532, 490587, 490820, 492105, 497121, 497150, 497516, 498721, 498722, 498723, 499414, 499415, 499416, 500297, 500409, 501269, 501892, 502314, 502575, 502725, 503162, 503785, 503838, 504888, 505098, 505111, 505893, 505954, 507594, 508393, 508445, 508723, 510812, 510813, 511767, 511791, 512675, 512676, 512870, 513533, 513979, 514192, 514193, 514197, 514198, 514216, 514217, 515265, 515357, 515535, 515546, 515548, 516392, 517357, 517812, 518033, 518931, 520423, 520723, 520724, 521768, 522038, 523141, 526001, 527534, and 528762. Other All antagonists include those disclosed in International Patent Application, Publication Nos. WO 91/00277, WO 91/00281, WO 91/11909, WO 91/11999, WO 91/12001, WO 91/12002, WO 91/13063, 91/15209, WO 91/15479, WO 91/16313, WO 91/17148, WO 91/18888, WO 91/19697, WO 91/19715, WO 92/00067, WO 92/00068, WO 92/00977, WO 92/02510, WO 92/04335, WO 92/04343, WO 92/05161, WO 92/06081, WO 92/07834, WO 92/07852, WO 92/09278, WO 92/09600, WO 92/10189, WO 92/11255, WO 92/14714, WO 92/16523, WO 92/16552, WO 92/17469, WO 92/18092, WO 92/19211, WO 92/20651, WO 92/20660, WO 92/20687, WO 92/21666, WO 92/22533, WO 93/00341, WO 93/01177, WO 93/03018, WO 93/03033 and WO 93/03040.

The contents of the aforesaid European and International Patent Applications are hereby incorporated by reference thereto.

AT II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention include, but are not limited to, compounds with the following generic names: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan.

Particularly preferred AT II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil. Candesartan and candesartan cilexetil are known from European Patent No. 459 136 B1, US 5,196,444 and US 5,703,110 to Takeda Chemical Industries. Candesartan cilexetil is currently manufactured and sold world-wide by AstraZeneca and Takeda.e.g. under the trade names Atacand®, Amias® and Blopress®.

NEP/ACE-inhibitors or pharmaceutically acceptable derivatives thereof, including active metabolites, which can be used for the prevention of stroke, diabetes and/or CHF include, but is not limited to, those compounds disclosed in U.S. Patents Nos. 5,508,272, 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 5,552,397, 4,749,688, 5,504,080, 5,612,359, 5,525,723, 5,430,145, and 5,679,671, and European Patent Applications 0481522, 0534263, 0534396, 0534492 and 0671172.

Preferred NEP/ACE inhibitors for use in the present invention are those which are designated as preferred in the above U.S. patents and European Patent Applications and are incorporated herein by reference. Especially preferred is the NEP/ACE inhibitor omapatrilat (disclosed in U.S. Patent No. 5,508,272), or MDL100240 (disclosed in U.S. Patent No. 5,430,145).

Renin-inhibitors or pharmaceutically acceptable derivatives thereof, including active metabolites, which can be used for the prevention of stroke, diabetes and/or CHF include, but is not limited to, the following compounds:

enalkrein; RO 42-5892; A 65317; CP 80794; ES 1005; ES 8891; SQ 34017; CGP 29287; CGP 38560; SR 43845; U-71038; A 62198; and A 64662.

Pharmaceutical formulations

In one aspect, the present invention relates to pharmaceutical formulations comprising as active ingredient an RAS inhibitor or a pharmaceutically acceptable derivative or prodrug thereof, including metabolites, for use in the prevention of stroke, diabetes and/or congestive heart failure (CHF).

For clinical use, the RAS inhibitor is formulated into a pharmaceutical formulation for oral, intravenous, subcutaneous, tracheal, bronchial, intranasal, pulmonary, transdermal, buccal, rectal, parenteral or some other mode of administration. The pharmaceutical formulation may contain the inhibitor in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

In the preparation of the pharmaceutical formulations of the present invention the active ingredient may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets.

The active ingredient may be separately premixed with the other, non-active ingredients, before being mixed to form a formulation.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active ingredient of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active ingredients. Hard gelatine capsules may also contain the active ingredients in combination with solid powdered ingredients such as

lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing the active ingredients and the remainder consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, preservatives, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a formulation of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients, preservatives and/or buffering ingredients. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent before use.

The total amount of active ingredient suitably ranges from about 0.1 % (w/w) to about 95 % (w/w) of the formulation, suitably from about 0.5 % to about 50 % (w/w) and can range from about 1 % to about 25 % (w/w).

The pharmaceutical formulations may contain from about 0.1 mg to about 1000 mg of active ingredient, preferably from about 1 mg to about 100 mg of active ingredient.

The dose of the active ingredient to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will suitably range from about 0.01 mg/kg to about 20 mg/kg, and can be range from about 0.1 mg/kg to about 10 mg/kg.

The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician. In general, dosages, and especially oral and parenteral dosages, can range from about 0.1 to about 100 mg per day of active ingredient, and can range from about 1 to about 50 mg per day of active ingredient.

The following Example is intended to illustrate, but in no way limit the scope of the invention.

EXAMPLE

A large-scale clinical trial was designed to examine the effect of the ACE inhibitor ramipril versus placebo in reducing cardiovascular events.

The study was conducted in 267 centres in 19 countries over a six year period and included 9,541 participants who are at high risk for cardiovascular events due to a history of previous ischaemic heart disease, stroke, peripheral arterial disease or individuals with diabetes.

The systolic blood pressure at inclusion of the patients was on average 138 mm Hg and thus the patients were normotensive at study start. After one month of therapy with either ramipril or placebo, the systolic blood pressure had decreased by 5.48 mm Hg and 1.59 mm Hg, respectively.

The primary endpoint of the study was myocardial infarction (MI), stroke and cardiovascular (CV) death (mortality).

The study was stopped early because of a very clear reduction in the combined endpoint of cardiovascular deaths, heart attacks and strokes in patients taking ramipril. In addition to the above benefits, there was also a reduction of between a fourth and a fifth in the need for revascularisation procedures (such as coronary artery bypass graft surgery, balloon angioplasty, etc.) and diabetic complications.

There was a clear 32% reduction in the ramipril group in the number of patients who developed a stroke, and this is surprising since patients were normotensive when recruited to the study.

The number of patients who developed CHF was significantly reduced by 21% in the ramipril group, which is unexpected since patients had no signs or symptoms of CHF at study start.

Equally surprising is the marked 36% reduction in the number of patients who developed diabetes in the ramipril group.

Abbreviations

ACE = angiotensin converting enzyme

AT II = angiotensin II type 1 receptor

CHF = congestive heart failure

IDMM = insulin-dependent, diabetes mellitus

JNC = Joint National Committee

MI = myocardial infarction

NIDDM = non-insulin-dependent diabetes mellitus

WHO = World Health Organization